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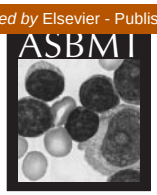

Autologous Stem Cell Transplantation for Small Cell Lung Cancer

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ABSTRACT

Small cell lung cancer usually responds to radiation and chemotherapy, but cures are infrequent. Autotransplantation attempts to increase cures by intensifying the effects of chemotherapy. We studied 103 patients receiving high-dose chemotherapy with autologous hematopoietic stem cell transplantation (SCT) for small cell lung cancer in 1989-1997 at 22 centers participating in the Autologous Blood and Marrow Transplant Registry. Median age at transplantation was 50 years (range, 30-74 years). Fifty-five percent of patients were men. Forty-seven percent of patients underwent transplantation in 1989-1993 and 53% in 1994-1997. Most patients received peripheral blood stem cells alone (39%) or with bone marrow (44%); 18% received bone marrow alone. The 2 most common preparative regimens were cyclophosphamide/carmustine/cisplatin (CBP) (60%) and ifosfamide/carboplatin/etoposide (ICE) (28%). Median time from diagnosis to transplantation was 6 months (range, 1-34 months). Most patients underwent transplantation after partial response (66%) or complete response (27%) to combination therapy. The 100-day mortality was 11% (95% confidence interval [CI], 6%-18%). Three-year probabilities of survival and progression-free survival (PFS) were 33% (95% CI, 24%-44%) and 26% (95% CI, 17%-36%), respectively, for all patients. Factors negatively associated with outcome in multivariate analysis were age greater than 50 years, extensive-stage disease at presentation, and preparative regimens other than CBP or ICE. Three-year survival and PFS rates were higher in patients with limited versus extensive disease, 43% versus 10% ($P < .001$) and 35% versus 4% ($P < .001$), respectively. Patients older than 50 years had nearly twice the risk of death or progression as younger patients (relative risk, 1.7; 95% CI, 1.1-2.8). Autologous SCT produces long-term survival in some patients with small cell lung cancer; SCT outcomes appear better in young patients with limited-stage disease. Transplantation for patients with extensive disease does not appear to produce substantial benefit.

KEY WORDS

Autologous stem cell transplantation • Small cell lung cancer

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INTRODUCTION

In the United States, cancer is the second most common cause of death, and lung cancer is the leading cause of cancer death in men and women [1]. About 164,000 new cases of lung cancer were diagnosed in 2000. Fifteen percent to 25% of lung cancers are histologically small cell [1,2]. The distinction between small cell lung cancer (SCLC) and non–small cell lung cancer is important, because small cell tumors are more sensitive to chemotherapy. For patients with limited-stage SCLC (30%-40% of patients), defined as disease that is confined to 1 hemithorax and can be encompassed within a single radiation therapy port, the mainstay of treatment is chemotherapy and radiation [3]. Median survival after chemotherapy and radiation for patients with limited-stage SCLC is 18 to 24 months, with fewer than 25% of patients surviving longer than 5 years [3-6]. For patients with extensive disease, median survival is less than 9 months, with rare survivors beyond 5 years [4].

Because SCLC is sensitive to chemotherapy, attempts to improve treatment outcome have included using high-dose chemotherapy followed by stem cell support. The contribution of chemotherapy dose intensity to response and survival remains controversial. Seven randomized trials have evaluated dose intensity in SCLC, mostly in the extensive-stage setting [7-13]. Dose intensity of the high-dose arms varied from 1.2 to 2-fold that of the lower-dose arms. Statistically significant increases in response and survival were observed for the higher-dose arms, although the clinical benefit was modest. In the only randomized trial exclusively treating patients with limited-stage SCLC, Arriagada et al. [13] used 6 cycles of chemotherapy in which the first cycle was either standard dose or modestly intensified. Intensification (not requiring transplantation) resulted in a complete response (CR) and survival advantage. In the only randomized trial of high-dose therapy with autotransplantation, Humblet et al. [14] treated 101 SCLC patients with chemotherapy for 5 cycles without thoracic radiotherapy. Forty-five patients were eligible for randomization to 1 further cycle of either high-dose or conventional-dose therapy with cyclophosphamide, etoposide, and carmustine [14]. A clear dose-response effect was demonstrated. Conversion from partial response (PR) to CR occurred in about 77% of patients after high-dose therapy compared with none after conventional-dose treatment. The disease-free survival rate was significantly higher in the high-dose arm, with a trend toward improved survival. However, an 18% toxic death rate on the high-dose arm led the investigators to conclude that high-dose therapy should not be considered a standard therapy for SCLC. Moreover, chest radiotherapy was not given in this trial, and almost all patients who relapsed had disease recurrence in the chest.

More recent studies suggest that survival and disease-free survival rates after autotransplantation for SCLC have improved with better initial treatment at diagnosis and better supportive care posttransplantation. In the Dana-Farber Cancer Institute/Beth Israel Hospital experience, the 5-year disease-free survival rate for selected patients with limited-stage disease in CR or near-CR at the time of high-dose therapy was 52% (median follow-up period, 61 months) [15-17]. This evaluation of patients receiving autotransplantation for SCLC reported to the Autologous Blood and Marrow Transplant Registry (ABMTR) was undertaken to identify patients most likely to benefit from high-dose therapy and to evaluate the most commonly used transplantation strategies.

MATERIALS AND METHODS

Autologous Blood and Marrow Transplant Registry

The ABMTR is a voluntary organization of more than 200 institutions that perform autotransplantations, primarily in the United States, Canada, and Central and South America. Centers report data on consecutive autotransplantations to a Statistical Center at the Medical College of Wisconsin.

Data Collection

The ABMTR began data collection in 1992. Data were collected retrospectively for patients who received autotransplants between 1989 and 1992 and prospectively thereafter. Participating centers register consecutive autotransplantations for all disease indications. Based on data collected in a recently conducted survey of all US transplantation centers, 50% to 60% of autotransplantations in North America are registered with the ABMTR [18].

The ABMTR collects data at 2 levels: registration and research. Registration data include disease type, age, sex, pretransplantation disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow and/or blood-derived stem cells), high-dose conditioning regimen, posttransplantation disease progression and survival, development of a new malignancy, and cause of death. Requests for data on progression or death for registered patients are made at 6-month intervals. All ABMTR teams contribute registration data. Research data are collected on subsets of registered patients, including comprehensive pre- and posttransplantation clinical information such as tumor size and pathology, sites of disease, smoking status, all cancer treatments before and after transplantation, clinical status (including cardiac, pulmonary, renal, and liver function) before and after transplantation, doses of high-dose therapy, blood or marrow graft treatment, and sites of posttransplantation progression.

Patients

Thirty-nine teams registered 132 patients with SCLC who received autotransplants between January 1, 1989, and December 31, 1997. This analysis includes the 103 patients in 22 teams for whom research data were available (see above). Participating centers are listed in the "Acknowledgments." Comparison of the 103 patients with research data to the 29 patients with only registration data showed the 2 groups to be similar in age, sex, race, disease status at transplantation (eg, CR, PR), year of transplantation, and interval from diagnosis to transplantation. Registration-only patients were less likely to have received stem cells from both blood and bone marrow than were the patients included in the study (12% versus 39%, $P = .04$). Limited-stage disease was defined as tumor confined to 1 hemithorax and regional lymph nodes (including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular lymph nodes) and ipsilateral pleural effusions (whether or not they were cytologically positive). Extensive-stage disease was defined as any level of disease not meeting the definition of limited-stage disease. CR was defined as no evidence of residual tumor at the primary or metastatic sites. PR was defined as a decrease

in size by 50% or greater at all measurable disease sites. Patients experiencing a reduction in primary tumor size by 90% to 99% with either no metastatic tumor (scar may be present) or mediastinal nodes less than 1.5 cm were considered to be very good partial responders (VGPR).

Statistical Methods

The primary outcomes were overall survival and progression-free survival (PFS) calculated from the day of transplantation. Events were death, progression, and, for patients with CR, recurrence of lung cancer. Individuals alive without progression or recurrence were censored at last follow-up. Univariate probabilities of survival, PFS, and 100-day mortality (death from any cause in the first 100 days after transplantation) were calculated using the Kaplan-Meier product-limit estimator [19,20]. Variables were tested in univariate analysis for their association with death and treatment failure (the inverse of PFS) using Cox proportional hazards regression [21]. Variables considered were age (above or below the median), sex, Karnofsky performance status at transplantation (<90% versus ≥90%), weight loss (<5% versus ≥5%), smoking history, lactate dehydrogenase (LDH) elevation at presentation, stage of disease at presentation (limited versus extensive), number of chemotherapy regimens, whether or not pretransplantation chemotherapy contained platinum, number of chemotherapy cycles, best response to initial chemotherapy, disease status at transplantation, pretransplantation thoracic radiation, pretransplantation cranial radiation, interval from diagnosis to transplantation, conditioning regimen, source of stem cells, year of transplantation, and use of growth factors to enhance recovery. For the final multivariate model, forward stepwise selection was used to select variables; a *P* value less than .05 was considered statistically significant. First-order interactions of variables in the final model were also checked. Using a time-dependent covariate approach, we checked all variables to ensure that the assumption of the Cox model was valid. A score test [22] was used to determine whether any center-specific effects required adjustment.

Planned Radiation after Transplantation. Studying effects of posttransplantation maneuvers on outcome, such as posttransplantation radiation therapy, must account for bias introduced by early deaths occurring before intended treatments were administered; ie, patients who die before planned radiation treatments can be administered would be considered in the no-treatment group even though such treatment was planned. This bias artificially increases the proportion of adverse events in the no-treatment group if all patients are considered from the time of transplantation. This bias was overcome by studying effects of posttransplantation cranial and thoracic radiation therapy only in patients already surviving more than 100 days after transplantation.

RESULTS

Patient characteristics are shown in Table 1. The median age at transplantation was 50 years, and 55% of the patients were men. Seventy-three percent of the patients had limited-stage disease at diagnosis, a rate that is somewhat higher than would be expected in an unselected population of SCLC patients. Only 21% of patients had more than 20 pack-years of smoking history; 14% continued to smoke after diagnosis. More than 90% of patients underwent initial chemotherapy management with a platinum-based regimen, with 54% of patients receiving 4 or fewer cycles of chemotherapy pretransplantation. Seventy-nine percent of patients experienced either a VGPR (50%) or CR (29%) to their initial chemotherapy regimen. Fifty-five percent of patients received thoracic radiation, and 6% received cranial radiation before transplantation. Only 7% of patients experienced relapse pretransplantation. Ninety-four patients (93%) underwent autologous transplantation as part of their initial management of SCLC. Median time from diagnosis to transplantation was 6 months (range, 4-34 months). Only 3 patients had an interval from diagnosis to transplantation greater than 1 year. Each had experienced a pretransplantation relapse after an initial response.

The most common high-dose regimens were cyclophosphamide, carmustine, and cisplatin (CBP) (60%) or ifosfamide, carboplatin, and etoposide (ICE) (28%). Bone marrow was the sole stem cell source in 18% of patients, and blood was the sole source in 39%. Forty-four percent of patients received both blood and bone marrow stem cells. Growth factors were used to promote hematopoietic recovery in 81% of patients. Planned posttransplantation thoracic radiation was delivered to 33% of the patients, whereas planned posttransplantation cranial irradiation was given to 64% of patients.

Median time to neutrophil recovery (0.5×10^9 cells/L) was 11 days (range, 7-47 days). The probability of death within 100 days was 11% (95% confidence interval [CI], 6%-18%) for the entire group. Causes of death within 100 days were toxicity (n = 5), recurrence (n = 2), infection (n = 2), hemorrhage (n = 1), and interstitial pneumonitis (n = 1). Among the 50 patients who died 100 days or longer after transplantation, the primary causes of death were progressive disease (n = 43), myocardial infarction (n = 1), and not specified (n = 6). The 3-year probability of PFS was 26% (95% CI, 17%-36%). Whereas 14 (30%) of 46 patients with VGPR to pretransplantation therapy converted to CR with transplantation, no patient with PR had a CR with transplantation.

The median time to relapse or progression was 18.6 months (95% CI, 11 to >36 months) for patients with limited disease and 8.6 months (95% CI, 5-11 months) for patients with extensive disease. The median survival and PFS rates for patients with limited-stage disease were 23.5 months (95% CI, 14.5-80 months) and 13.8 months (95% CI, 10.4-30 months), respectively.

Patients with limited-stage disease had 3-year probabilities of survival and PFS of 43% (95% CI, 31%-54%) and 35% (95% CI, 23%-47%), respectively. Corresponding probabilities for patients with extensive disease were 10% (95% CI, 13%-45%) (Table 2, Figure 1) and 4% (95% CI, 1%-16%) (Table 2, Figure 2).

Table 3 shows the results of multivariate analyses of factors associated with overall survival and PFS. Extensive-stage disease at presentation and age greater than 50 years were significant adverse prognostic factors for both overall survival and PFS. High-dose chemotherapy with either CBP or ICE conferred a similar prognosis. Once these factors were considered in the multivariate models, primary tumor

Table 1. *Patient, Disease, and Transplantation Characteristics of 103 Patients with SCLC Reported to the ABMTR between 1989 and 1997 by 22 Teams Worldwide*

Variable	No. (%)
No. of patients	103
No. of reporting centers	22
Year of transplantation	
1989-1991	18 (18)
1992-1994	41 (39)
1995-1997	44 (43)
Age at transplantation, median (range), y	50 (30-66)
Sex	
Male	57 (55)
Female	46 (45)
Smoking history	
≤20 packs/y	81 (79)
>20 packs/y	22 (21)
Performance score pretransplantation	
90%-100%	62 (60)
<90%	39 (38)
Stage	
Limited	75 (73)
Extensive	28 (27)
Histology	
Small cell	97 (94)
Mixed small/non–small cell	6 (6)
Tumor stage	
Tis	2 (2)
T1	12 (13)
T2	28 (30)
T3	22 (23)
T4	31 (32)
Lymph node stage	
None	6 (6)
N1	5 (5)
N2	40 (42)
N3	44 (46)
LDH at presentation	
Normal	79 (77)
Elevated	24 (23)
Surgery included in initial management	
No	101 (99)
Yes	1 (1)
Chemotherapy as initial management	
Platinum-based	94 (91)
Non–platinum-containing	9 (9)
No. of cycles chemotherapy pretransplantation	
≤4 cycles	55 (54)
5 or more cycles	48 (47)
No. of chemotherapy regimens	
1	88 (85)
2 or more	15 (15)
Best response to initial regimen	
CR	29 (29)
VGPR (90%-99% decrease)	50 (50)
PR	19 (19)
Stable disease	2 (2)
Initial thoracic radiotherapy	
Yes	56 (55)
No	46 (45)
Initial cranial irradiation	
Yes	6 (6)
No	95 (94)
Any relapse pretransplantation	
Yes	7 (7)
No	94 (93)
Disease status at conditioning	
CR	28 (27)
VGPR	49 (48)
PR	19 (18)
Stable disease	2 (2)
Progressive disease	5 (5)
Conditioning regimen	
Cyclophosphamide/carmustine/cisplatin	62 (60)
Ifosfamide/carboplatin/etoposide	29 (28)
Other*	12 (12)
Graft type	
Bone marrow	18 (18)
Peripheral blood stem cells	40 (39)
Bone marrow + peripheral blood stem cells	45 (44)
Interval from diagnosis to transplantation, median (range), mo	6 (4-34)
Growth factors for recovery	
Yes	83 (81)
No	20 (19)
Follow-up of survivors, median (range), mo	40 (3-96)
Planned radiation therapy after transplantation	
Thoracic	14 (33)
Cranial	27 (64)
Other	1 (3)

*Carmustine (BCNU)/etoposide/thiotepa (n = 2); cyclophosphamide/BCNU/etoposide (n = 2); busulfan/thiotepa/melphalan (n = 1); carboplatin/melphalan/etoposide (n = 1); cyclophosphamide/carboplatin (n = 1); cyclophosphamide/thiotepa (n = 1); and carboplatin (n = 1).

size, best response to initial chemotherapy, and radiation therapy pretransplantation or posttransplantation (cranial or thoracic) were not significantly associated with overall survival or PFS. Table 2 shows the 3-year probabilities of overall survival and PFS according to prognostic factors identified in the multivariate analysis.

DISCUSSION

SCLC is known to be sensitive to several chemotherapeutic agents, with a high rate of initial response. However, despite initial response, about 40% to 47% of patients with limited-stage disease and fewer than 5% of patients with extensive-stage disease at presentation survive longer than 2 years [3-6]. Relapse-related mortality continues to occur beyond 2 years. Consolidation of early responses with high doses of chemotherapy followed by autologous hematopoietic stem cell rescue has been performed with the intent to decrease this high recurrence rate.

Multiple previous small phase I and II studies of autologous transplantation for SCLC have been reported [23-30]. Results in patients undergoing transplantation for refractory or recurrent disease have been dismal. When given as initial therapy for SCLC, results have been no better than those reported with conventional chemotherapy alone. However, autologous transplantation used as intensification for patients responding to first-line chemotherapy has shown

Table 2. *Probability of Survival and Progression-Free Survival in Selected Groups*

Variable	No. of Patients Evaluable	3-Year Probability of Survival (95% CI)	*P*	3-Year Probability of PFS (95% CI)	*P*
Stage of disease at presentation			**<.001**		**<.001**
Extensive	**28**	**10 (2-25)**		**4 (1-16)**	
Limited	**75**	**43 (31-54)**		**35 (23-47)**	
Age at transplantation			**.04**		**.18**
≥50 y	**54**	**22 (10-37)**		**22 (11-35)**	
<50 y	**49**	**46 (32-59)**		**30 (17-44)**	

promise in some studies. Early case series, all small, suggested no significant benefit of high-dose compared to conventional chemotherapy. However, treatment-related mortality during the period of those studies was higher than the mortality expected with current supportive care techniques. Humblet et al. reported a significant improvement in the disease-free survival rate for patients randomized to autotransplantation compared to conventional therapy, but this trial was flawed by a low randomization rate, small numbers of patients, and high treatment-related mortality (18%) [14]. Moreover, patients in the transplantation arm did not have an improvement in overall survival.

More recent trials of autotransplantation for patients with extensive disease provide little encouragement. Jennis et al. reported a small trial of 10 patients with extensive-stage disease at transplantation; all patients relapsed at a median time of 4 months [31]. Likewise, patients with extensive disease treated by Tomeczko et al. and Elias had high rates of relapse [32,33]. Not surprisingly, patients with limited-stage disease appear to have better disease-free and overall survival rates than those receiving transplants for extensive disease. Studies by Elias et al., Tomeczko et al., and Brugger et al. all report high response rates, with 2- or 3-year disease-free survival rates of 25% to 57% in patients with limited-stage disease [17,32,34].

Few patients receive autologous transplantation for SCLC. Our series of 103 autotransplantations for SCLC at multiple centers represents a substantial proportion of the procedures performed in the United States from 1989 to 1997. Our results indicate that for patients with limited-stage disease, the 3-year probabilities of overall survival and PFS were 43% and 35%, respectively. Although this is not a comparative study, the 3-year survival results from autotransplantation are similar to the 2-year survival results reported in large trials of chemotherapy/radiotherapy alone for limited-stage disease [3-6,35]. However, the median survival and PFS in our patients are only slightly longer than those reported in the same large trials, 19 to 21 months for overall survival and 12 months for PFS, and fall within the reported confidence intervals for these medians [3,5,6]. Thus, consolidation with autologous transplantation may offer a small improvement in long-term survival of some patients with limited-stage disease based on 3-year survival probabilities. However, longer follow-up of this cohort of transplantation patients is required to determine whether patients receiving stem cell transplantation for limited-stage disease experience lower late-failure rates than do patients receiving conventional therapy.

Unfortunately, our findings confirm that the prognosis after autotransplantation for patients with extensive-stage disease remains dismal, with 3-year probabilities of overall survival and PFS of 10% and 4%, respectively.

Reported adverse prognostic factors for patients with SCLC treated with chemotherapy alone include poor performance score, male sex, and extensive-stage disease [36-38]. Our study found that adverse prognostic factors for PFS and survival after autologous transplantation include age greater than 50 years and extensive-stage disease. The 2 most

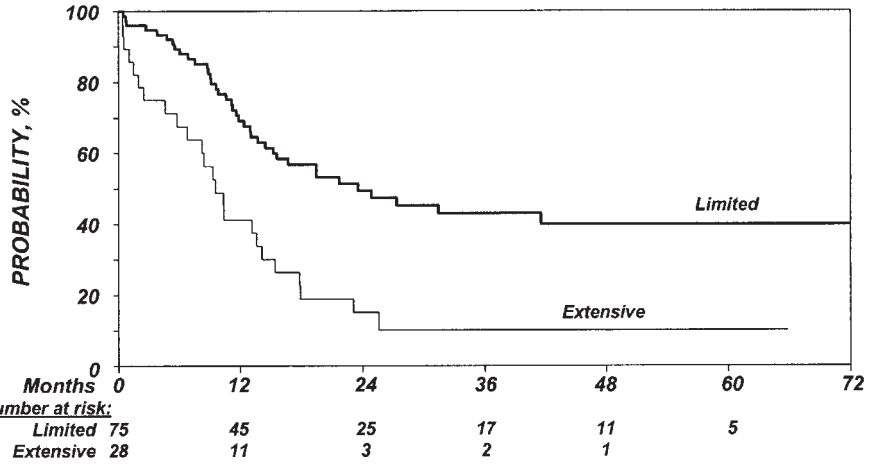

Figure 1. Probability of survival by extent of disease.

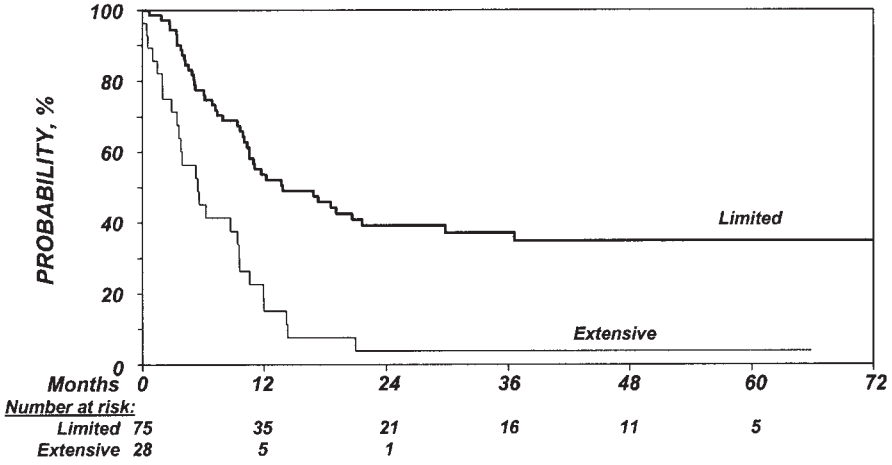

Figure 2. Probability of progression-free survival by extent of disease.

commonly used high-dose chemotherapy regimens, CBP and ICE, appear to produce similar results. Although patients receiving regimens other than CBP or ICE had a worse prognosis in our models, the small number of patients receiving different regimens makes it impossible to conclude that one or more of them may not be equal or better than ICE or CBP. Likewise, because the number of patients in the overall study is small, it is possible that a small difference between ICE and CBP exists but was not detected. Although response to induction chemotherapy was previously reported to significantly predict outcome for patients with limited-stage disease [17], we could not reproduce that finding in this study.

One limitation of this study is potential selection bias. As an observational database of transplant recipients, the ABMTR has no way of knowing which patients with limited or extensive disease were evaluated by participating transplantation centers but not considered to be reasonable transplantation candidates. Secondly, 68 patients analyzed in this study received their transplant at a single center. Although it is possible that our results are driven by the experience of a single center, statistical tests suggest that there was no effect of transplantation center on the main outcomes of the study.

Although the results of this analysis suggest that stem cell transplantation for patients with limited-stage disease offers minimal improvement in overall survival rate, only a randomized clinical trial can appropriately answer the question of whether autologous transplantation is superior to conventional treatment regimens. Furthermore, a trial directly comparing conventional chemotherapy/radiotherapy with autologous stem cell transplantation would be ideal to compare toxicities of therapy. It is conceivable that stem cell transplantation offers similar or slightly improved survival with similar toxicity to combined modality conventional therapy, which is associated with as much as 7% risk of fatal pneumonitis [6] and substantial esophageal and pulmonary toxicity [3,6].

Large database studies can help identify optimal patient groups that should be investigated further in clinical trials. In our study, limited-stage disease, age less than 50 years, and high-dose therapy with either CBP or ICE were found to be significant predictors of survival and PFS after transplantation for SCLC. We conclude that patients with limited-stage disease who are younger than 50 years should be studied in a randomized trial that compares best conventional therapy with transplantation after induction therapy. Ideally, such a phase III trial would also include toxicity and quality-of-life endpoints in addition to the usual outcomes of response and PFS. In this way, the field can move beyond pilot studies to definitively address the role of dose intensification.

Table 3. *Factors Significantly Associated with Survival or Progression-Free Survival in Multivariate Analyses*

Variable	No. of Patients Evaluable	Relative Risk for Death (95% CI)	*P*	Relative Risk for Progression or Death (95% CI)	*P*
Stage of disease at presentation					
Extensive	**28**	**1.0**		**1.0**	
Limited	**75**	**0.37 (0.20-0.68)**	**.001**	**0.36 (0.21-0.64)**	**<.001**
Age at transplantation					
≥50 y	**54**	**1.0**		**1.0**	
<50 y	**49**	**0.47 (0.28-0.78)**	**.004**	**0.58 (0.36-0.94)**	**0.03**
Preparative regimen			**.01***		**.002***
CBP	**62**	**1.0**		**1.0**	
ICE	**29**	**1.34 (0.70-2.53)**	**.37**	**1.70 (0.95-3.04)**	**.07**
Others	**12**	**3.42 (1.54-7.60)**	**.003**	**3.82 (1.78-8.19)**	**<.001**

*Wald 2 degree of freedom test for overall significance of variable.

One randomized trial comparing conventional chemotherapy with high-dose chemotherapy for SCLC is underway in Europe [39]. This trial will compare patients with either limited or extensive disease treated with conventional-dose ICE to those treated with 2 cycles of epirubicin/paclitaxel followed by 3 courses of high-dose ICE with stem cell support. All patients in CR will receive posttransplantation thoracic irradiation and prophylactic cranial irradiation. Researchers conducting this study hope to accrue 430 patients over 3 years.

A limitation to completion of clinical trials for SCLC, however, may be the rate of accrual to the high-dose arm following conventional induction. In a recent observational study reported by Fetscher et al., only 58% of enrolled patients with limited disease completed standard and high-dose chemotherapy [40].

Although it is hoped that the results of a randomized trial will establish more clearly whether SCT has a role in the treatment of SCLC, especially for patients with limited-stage disease, overall results have been disappointing. Innovative approaches are required in the management of this disease, particularly for patients who present with extensive-stage disease.

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Transplantation Centers Providing Data for This Analysis

University of Nebraska Medical Center, Omaha, NE; Case Western Reserve University Hospital, Cleveland, OH; University of Pittsburgh, Pittsburgh, PA; James Graham Brown Cancer Center, University of Louisville, Louisville, KY; H. Lee Moffitt Cancer Center, Tampa, FL; Dana Farber Cancer Institute, Boston, MA; Dartmouth-Hitchcock Medical Center, Lebanon, NH; Walter Reed Army Medical Center, Washington, DC; Baptist Hospital of Miami, Miami, FL; St. Francis Regional Medical Center, Wichita, KS; State University of New York Health Science Center, Syracuse, NY; Institute Nacional de Cancerologia, San Fernando, Mexico; University of California, San Diego, San Diego, CA; Hoag Cancer Center, Newport Beach, RI; Cancer and Blood Institute of the Desert, Rancho Mirage, CA; Gulhane Military Medical Academy, Ankara, Turkey; Roger Williams Cancer Center, Providence, RI; University of Massachusetts Medical Center, Worcester, MA; Arlington Cancer Center, Arlington, TX; Georgetown University Medical Center, Washington, DC; Washington University School of Medicine, St. Louis, MO; Missoula Oncology & Infectious Disease, Missoula, MT.

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